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Beyond Traditional Outcomes: Improving Quality of Life in Patients with Renal Cell Carcinoma

DAVID CELLA

Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Illinois, USA

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ABSTRACT

The introduction of molecular targeted therapies for patients with metastatic renal cell carcinoma has provided treatment options that are more efficacious and better tolerated than cytokine therapy, the previous standard of care. These advances have led to renewed efforts to define the health-related quality of life (HRQOL) impact of disease status stabilization or improvement versus that of treatment-associated adverse events. The distinct classes of targeted agents have unique AE profiles related to their specific targets; therefore, treatment considerations should include the patient's pretreatment HRQOL along with the known HRQOL effects of each drug. With more second- and third-line treatment options available for patients with metastatic renal cell carcinoma, HRQOL outcomes in earlier lines of therapy may guide treatment decisions for subsequent therapy, as poor HRQOL at therapy onset predicts poor survival. Both general and disease-specific instruments are used in clinical trials to reveal the impact of treatment on patient-reported outcomes. In this article, the common instruments used to assess HRQOL and the HRQOL outcomes observed in pivotal trials of targeted therapies are reviewed. Current data indicate that first-line therapy with sunitinib and first-line therapy in poor-prognosis patients with temsirolimus provide improved HRQOL compared with interferon-α. First- and second-line therapy with pazopanib and second-line therapy with everolimus and sorafenib maintained HRQOL levels similar to placebo, indicating that these agents do not worsen HRQOL. The HRQOL effects of bevacizumab plus IFN-α have not been reported. As new agents enter clinical investigation, HRQOL data can help determine their overall role in treatment. ***The Oncologist*** 2011;16(suppl 2):23–31

INTRODUCTION

Health-related quality of life (HRQOL) is an important outcome of cancer therapy, particularly in poor-prognosis populations receiving palliative treatment. Given the generally poor prognosis of patients with metastatic renal cell carcinoma (mRCC) and the toxicity associated with therapy, HRQOL has become an increasingly important outcome in this patient population.

Until late 2005, cytokine therapy with interleukin-2 (IL-2) or interferon-alpha (IFN-α) was the only treatment

Correspondence: David Cella, Ph.D., Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Abbott Hall – Suite 729, Chicago, Illinois 60611, USA. E-mail: d-cella@northwestern.edu Received September 23, 2010; accepted for publication December 20, 2010. 1083-7159/2011/$30.00/0 doi: 10.1634/theoncologist.2011-S2-23

option for patients with mRCC and was associated with considerable toxicity, negatively influencing patient HRQOL [1, 2]. Since then, the ongoing introduction of molecular targeted therapies for mRCC has provided treatment options that are more efficacious and better tolerated than cytokine therapy. However, such agents also are associated with toxicities that may affect patient HRQOL. Thus, both the efficacy of molecular targeted therapies to relieve disease symptoms, the tolerability of treatment-related adverse events (AEs), and the ability of interventions to manage treatment-related AEs will influence patient HRQOL outcomes with these agents. In addition, the HRQOL effects of first-line therapy may influence the choice of second-line therapy. Given the overall survival (OS) benefits observed with newer targeted therapies for mRCC, the effect of these agents on HRQOL is of particular interest.

This article discusses the assessment of HRQOL outcomes observed in the recently published pivotal trials of molecular targeted therapies for mRCC and will include a description of the common general and disease-specific instruments used to assess HRQOL in patients with mRCC.

Assessing HRQOL in mRCC Patients

Evolving HRQOL Issues with New Therapeutic Options

Patients with advanced mRCC face several issues that may impair their HRQOL. In a national, cross-sectional study of patients with RCC, the top five symptoms reported by patients with metastatic disease were fatigue, weakness, worry, shortness of breath, and irritability [3].

Disease-Related HRQOL Issues

HRQOL issues related to tumor burden include anorexia-cachexia syndrome which, in addition to weight loss and lethargy, may involve fever, night sweats, and dysgeusia; anemia, which is often a presenting symptom; hypercalcemia, which may cause confusion and constipation; pain (somatic, visceral, and neuropathic); and venous thromboembolism. In addition, metastases are associated with symptoms specific to the site involved; for example, lung metastases may cause airway obstruction, bleeding, and dyspnea [4]. The psychosocial impact of diagnosis with an incurable, poor-prognosis malignancy such as mRCC also is considerable. Among patients participating in a study to develop a kidney cancer–specific symptom index, patient-identified psychosocial concerns included emotional distress, losing hope, worry about the illness progressing, and HRQOL concerns [5].

Treatment-Related HRQOL Issues in the Immunotherapy Era

Side effects of cytokine therapy include fatigue, peripheral neuropathy, mood disruption, endocrine dysfunction, and autoimmune-mediated thyroid dysfunction [1, 2, 6]. Psychosocial function subscale scores of the Short Form-12 (SF-12), a general instrument for HRQOL assessment, were significantly lower in immunotherapy-treated mRCC patients than those in the general population and those in patients with breast cancer, non-breast female cancer, and non-prostate male cancer [2]. However, in a study of immunotherapy-treated progressive mRCC in 22 outpatients with low/intermediate risk disease, an interesting association between rapid HRQOL decline and OS rate was seen. After 3 weeks of at-home therapy with low-dose IL-2 + IFN-α2a + 13-cis-retinoic acid, those patients who achieved a complete response (CR) to therapy had the most prominent decreases from baseline in HRQOL, caused mainly by decreases in physical functioning, psychological distress, impairment of social activities, and limitation in working capacity. The investigators hypothesized that these results were related to the underlying mechanism of immunotherapy-based treatment, such that patients with more intact immune systems experienced these HRQOL decreases because of exogenous cytokine-mediated immune activation [7].

Treatment-Related HRQOL Issues in the Targeted Therapy Era

The availability of new, effective treatment options for first-line and subsequent mRCC therapy has led to renewed efforts to define the relative HRQOL impact of disease status stabilization or improvement versus that of treatment-associated AEs. Results of a study in cytokine-pretreated patients receiving sunitinib or sorafenib suggested that poor HRQOL at the onset of targeted therapy for mRCC may be prognostic for poor survival. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) was completed by patients at baseline and weeks 4, 6, 10, 12, and 16. During the first 4 weeks of treatment, global HRQOL deteriorated significantly from baseline; however, at week 6, it increased significantly and stabilized at this level thereafter. Global quality of health at baseline was associated significantly with tumor response, and patients whose baseline scores were above the median value achieved significantly longer median progression-free survival (PFS) rates than those whose baseline scores were less than or equal to the median value (11.0 and 5.9 months, respectively; $p = .002$) [8]. Continued deterioration in HRQOL during therapy

Table 1. Instruments used to evaluate HRQOL in patients with mRCC

	No. of items	Description	Scoring
Kidney cancer–specific instruments			
FKSI			Likert: 0 = "not at all" to 4 = "very much"
FKSI-DRS [10]	9	Concise list of symptoms caused by RCC	
FKSI-10 [5]	10	List of symptoms and concerns of people with RCC	
FKSI-15 [5]	15	List of symptoms and concerns of people with RCC	
FKSI-19 [11]	19	Revised list of symptoms and concerns of people with RCC (FKSI-15 + 4 additional items)	
RCC Symptom Index [3]	30	List of signs and symptoms of RCC	Likert
Cancer-specific instruments			
FACIT			Likert
FACT-G [12]	27	Primary domains: physical well-being, social/family well-being, emotional well-being, functional well-being	
FACT-Fatigue [13]	40	A fatigue subscale containing 13 items + 27-item FACT-G	
FACT-BRM [14]	40	For patients receiving BRMs; physical and mental subscales containing 14 questions + 27-item FACT-G version 4	
General instruments			
EORTC QLQ-C30 [15]	30	Contains 5 functional scales (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, pain, nausea and vomiting), a global health scale, an HRQOL scale, and single items to assess common cancer symptoms and financial impact	Likert: yes/no; rankings from very poor (1) to excellent (7)
EuroQol [16]	16	Contains 6 domains: mobility, self-care, main activity, social relationships, pain, and mood	0 = worst imaginable health state; 100 = best
EQ-5D Index			
EQ-5D VAS			
SF-36 [17]	36	Contains 8 dimensions: physical function, role limit (physical), role limit (emotional), pain, general health perceptions, vitality, social functioning, emotional well-being	Likert

Abbreviations: BRM, biological response modifier; DRS, disease-related symptoms; EORTC, European Organization for Research and Treatment of Cancer; FACIT, Functional Assessment of Chronic Illness Therapy; FACT-G, Functional Assessment of Cancer Therapy-General; FKSI, FACT-Kidney Cancer Symptom Index; HRQOL, health-related quality of life; mRCC, metastatic renal cell carcinoma; QLQ, quality-of-life questionnaire; SF-36, Short Form-36; VAS, visual analog scale.

may serve as an early signal of underlying disease progression [9].

HRQOL Assessment Tools with Applicability to mRCC

Features of disease-specific and general HRQOL tools used to evaluate patients with mRCC are outlined in Table 1. Two validated HRQOL instruments are specific to RCC: the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI) [5] and the Renal Cell Carcinoma-Symptom Index [3]. The 15-item FKSI has several derivatives: the nine-item FKSI-Disease Related Symptoms (FKSI-DRS), which was designed specifically to assess only symptoms related to the disease [10]; an abbreviated 10-item version (FKSI-10) that, like the 15-item tool, contains items to assess both symptoms and concerns [5]; and a recent revision that contains the same items as the 15-item tool along with four additional items (FKSI-19) [11]. This most recent FKSI-19 was developed to be responsive to the requirements for the valid patient-reported outcomes assessment stated by the U.S. Food and Drug Administration. The Renal Cell Carcinoma-Symptom Index is a 30-item in-

Table 2. Common adverse events of approved molecular targeted agents for mRCC in pivotal trials

	Sunitinib	Sorafenib	Pazopanib	Temsirolimus	Everolimus
Common grade 3 or 4 AEs (≥5% of patients)	Neutropenia (18%) Lymphopenia (18%) Hypertension (12%) Fatigue (11%) Diarrhea (9%) HFS (9%) Asthenia (8%) Nausea (5%)	HFS (6%) Fatigue (5%)	Lymphopenia (5%)	Anemia (20%) Asthenia (11%) Hyperglycemia (11%) Dyspnea (9%) Infection (5%) Pain (5%)	Anemia (9%)
AEs leading to dose reduction	NR	NR	NR	NR	NR
AEs leading to treatment discontinuation	NR	Constitutional AEs GI-related AEs Dermatologic AEs Pulmonary/URT AEs	NR	NR	Pneumonitis Dyspnea Lung disorder
Reference	Motzer et al. [21]	Escudier et al. [22]	Sternberg et al. [23]	Hudes et al. [24]	Motzer et al [25]

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFS, hand–foot syndrome; mRCC, metastatic renal cell carcinoma; NR, not reported; URT, upper respiratory tract.

dex of signs and symptoms of patients with localized RCC and mRCC [3].

The Functional Assessment of Chronic Illness Therapy (FACIT) System contains the FACT-G (Functional Assessment of Cancer Therapy-General) [12], which may be used alone or may serve as the base for the FACT-Fatigue [13] and the FACT-Biologic Response Modifier (FACT-BRM) questionnaires [14]. These instruments, as well as the EORTC QLQ-C30 [15], are used in a variety of cancer populations. General HRQOL tools include the EuroQol health status measures (EQ-5D Index and EQ-5D Visual Analogue Scale [VAS]) [16], the Short-Form 36 Item Health Survey (SF-36) [17, 18], and Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) analyses [19].

HRQOL Data for Targeted Agents Approved for Treatment of RCC

As discussed in detail in the article in this supplement by Hutson [20], six molecular targeted agents are currently approved for the treatment of mRCC, including three multitargeted tyrosine kinase inhibitors (TKIs; sunitinib, sorafenib, and pazopanib), two mammalian target of rapamycin (mTOR) inhibitors (temsirolimus and everolimus), and one monoclonal antibody against vascular endothelial growth factor (VEGF) in combination with IFN-α (bevacizumab plus IFN-α). Available tolerability and HRQOL data for these agents are summarized below and in Tables 2–5; to date, no HRQOL data have been published for bevacizumab plus IFN-α in patients with mRCC.

Multitargeted TKIs

Sunitinib

In the phase III randomized pivotal clinical trial of sunitinib, patients received first-line therapy with oral sunitinib 50 mg/day (6-week cycles of 4 weeks on/2 weeks off) versus IFN-α2a (subcutaneous injection; 3 times weekly on nonconsecutive days). The key AE findings related to treatment delivery were as follows: (a) the rate of AE-related treatment discontinuations was 19% for sunitinib recipients and 23% for IFN-α recipients (specific attributable AEs were not reported) [21] and (b) the rate of dose reduction during sunitinib treatment was 50% compared with 27% during IFN-α treatment [21]. The specific AEs that necessitated the dose reductions were not reported. In addition, the percentage of patients in each group who required dose interruptions or delays was not reported.

The effects of sunitinib on HRQOL were assessed with the FKSI-DRS, the FKSI-15, the FACT-G, and the EuroQol assessments (EQ-5D Index and EQ-5D VAS) at base-

Table 3. HRQOL assessment methodology across pivotal trials of approved molecular targeted agents for mRCC

Sunitinib	Sorafenib	Pazopanib	Temsirolimus	Everolimus
● FKSI-DRS (primary HRQOL measure)	● FKSI-10 (primary HRQOL measure)	● EORTC QLQ-C30	● EQ-5D Index	● EORTC QLQ-C30
● FKSI-15	● FKSI-15	● EQ-5D Index	● EQ-5D VAS	● FKSI-DRS
● FACT-G	● FACT-G PWB	● EQ-5D VAS	● Q-TWiST	
● EQ-5D Index			● TWiST	
● EQ-5D VAS				
● TWiST				

Abbreviations: DRS, disease-related symptoms; EORTC, European Organization for Research and Treatment of Cancer; FACT-G, Functional Assessment of Cancer Therapy-General; FKSI, FACT-Kidney Cancer Symptom Index; HRQOL, health-related quality of life; mRCC, metastatic renal cell carcinoma; PWB, physical well-being; Q-TWiST, Quality-adjusted Time Without Symptoms or Toxicity; VAS, visual analog scale.

Table 4. Summary of HRQOL outcomes with approved multitargeted tyrosine kinase inhibitors for mRCC

Sunitinib (first-line)	Sorafenib (second-line)	Pazopanib (first- and second-line)
● Clinically meaningful differences in scores versus IFN-α (after cycle 4 for FKSI-DRS; at all cycles for all other measures)	● FKSI-10 total score did not differ significantly from placebo; maintained HRQOL similar to placebo	● Maintained HRQOL similar to placebo
● Fewer severe disease-specific symptoms than with IFN-α	● Improvement in some symptoms (coughing, loss of breath, fever, ability to enjoy life, worry)	
● Greater toxicity-adjusted PFS rate than with IFN-α	● Did not worsen amount of energy, fatigue, sleep quality, pain, weight loss	
	● Prolonged median time to health status deterioration	
	● Baseline FKSI predictive of OS rate	

Abbreviations: DRS, disease-related symptoms; FKSI, FACT-Kidney Cancer Symptom Index; HRQOL, health-related quality of life; IFN-α, interferon-alfa; mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression-free survival.

Table 5. Summary of HRQOL outcomes with approved mTOR inhibitors for mRCC

Temsirolimus (first-line/ poor-prognosis patients)	Everolimus (second-line)
● Greater quality-adjusted survival versus IFN-α	● Maintained HRQOL similar to placebo
	● Prolonged time to definitive deterioration in HRQOL and KPS score

Abbreviations: HRQOL, health-related quality of life; IFN-α, interferon-alfa; KPS, Karnofsky performance status; mRCC, metastatic renal cell carcinoma; mTOR, mammalian target of rapamycin.

line, on days 1 and 28 of each treatment cycle, and at the end of treatment/study withdrawal. The FKSI-DRS was the primary HRQOL endpoint, defined prospectively [26]. In the interim analysis, significantly better FKSI-DRS and FKSI-15 scores were associated with sunitinib versus IFN-α across all cycles [26]. After the first treatment cycle, FKSI-DRS and FKSI-15 scores decreased to lower than baseline in both treatment arms [26]. FKSI-DRS scores remained below baseline with IFN-α but increased slowly over time to above baseline with sunitinib [26]. Differences in mean FACT-G total and subscale scores significantly favored sunitinib over IFN-α across all cycles [26]. Sharp declines in FACT-G total scores and scores on the physical well-being and functional well-being (FWB) subscales were seen after cycle 1 for the IFN-α group, with a lesser deterioration in the physical well-being subscale for sunitinib [26]. Analyses with the EQ-5D Index and VAS yielded similar findings [26].

Final results were consistent with those reported for the interim analysis [27]. When trial results were analyzed geographically, the United States and European Union (EU) subpopulations showed similar outcomes on all endpoints

except for the FKSI item, "I am bothered by side effects of treatment," but within each geographic group, the treatment difference for this item was not significant [27]. Results of a TWiST analysis that included the highest frequency grade 3 or 4 treatment-related AEs (fatigue/asthenia, hypertension, diarrhea, nausea/vomiting, dermatitis/hand-foot syndrome, and depression) and defined overall benefit as PFS time adjusted for the number of days spent without treatment-related toxicity indicated that sunitinib provided greater toxicity-adjusted PFS rates than IFN-α [28]. Consequently, first-line treatment with sunitinib is associated with superior HRQOL compared with IFN-α.

Sorafenib

In the pivotal, phase III placebo-controlled trial of oral sorafenib in patients who had failed one prior systemic therapy, key AE findings related to treatment delivery were that 10% of sorafenib recipients had an AE-related treatment discontinuation (versus 8% of placebo recipients), with discontinuations attributed primarily to constitutional, gastrointestinal, dermatologic, or pulmonary-upper respiratory tract symptoms [22], and that rates of dose interruption and reduction were 21% and 13%, respectively, with sorafenib (versus 6% and 3%, respectively, with placebo [$p < .001$, sorafenib versus placebo]). Dose interruptions occurred mainly in response to dermatologic AEs (primarily hand-foot syndrome or rash) and gastrointestinal AEs (including diarrhea) [22].

HRQOL was evaluated with the FKSI-10 (primary HRQOL endpoint), the FKSI-15 (to measure changes in individual items), and the FACT-G PWB subscale on day 1 of each cycle and at the end of treatment [29]. No significant differences in HRQOL scores were noted between sorafenib and placebo during the first five treatment cycles [29]. Sorafenib significantly prolonged the time to health status deterioration compared with placebo as measured by the FKSI-10 and the FACT-G PWB subscale [29]. On the basis of an analysis of the individual components of the FKSI-15, individual symptoms and concerns were unchanged or significantly improved with sorafenib versus placebo, except for the item reflecting the bothersome side effects of treatment, which was significantly worse for the sorafenib group [29]. Sorafenib-treated patients reported less coughing, loss of breath, fevers, and worry about their disease and a greater ability to enjoy life [29]. Additional analyses determined that baseline scores on the FKSI-15 and on 11 of the 15 individual items were predictive of OS rates [29].

Results of a recently reported prospective, single-arm study of sorafenib in 85 cytokine-refractory Japanese patients support the conclusion that treatment with sorafenib does not impair HRQOL. SF-36 scores in patients who had received sorafenib for at least 3 months showed significant improvement from baseline in mental health; responders showed significant improvements in body pain, role limitations because of emotional problems, and mental health compared with patients who had not achieved a response; and the only scale with scores that differed significantly between patients with and without severe AEs was social function. In 26 patients who were followed for at least 12 months, scores at 3 months remained stable throughout follow-up [30].

Pazopanib

Orally administered pazopanib was evaluted in cytokine-pretreated and systemic treatment-naive patients in a randomized, placebo-controlled phase III pivotal trial. The key AE finding related to treatment delivery was that 14% of pazopanib recipients had an AE-related treatment discontinuation (versus 3% of placebo recipients). When the pazopanib-treated group was analyzed by prior treatment status, 19% of cytokine-pretreated pazopanib recipients and 12% of systemic treatment-naive patients discontinued treatment because of AEs [23]. Specific AEs leading to discontinuation were not reported. The median duration of exposure to pazopanib was 7.4 months; however, rates of dose interruption and dose reduction and specific attributable AEs were not reported [23].

The effects of pazopanib on HRQOL in these patients were evaluated with the EORTC-QLQ-C30 and the EuroQol assessments (EQ-5D Index and EQ-5D VAS) at baseline and at weeks 6, 12, 18, 24, and 48 [23]. No significant differences in scores on these instruments were noted between the pazopanib and placebo groups at any time point, indicating that treatment with pazopanib did not worsen HRQOL [23]. Patients with treatment-naïve advanced RCC currently are being enrolled into a phase III trial comparing pazopanib with sunitinib, with HRQOL as a secondary endpoint [31].

Table 4 provides a summary of the HRQOL data obtained with sunitinib, sorafenib, and pazopanib in their pivotal clinical trials.

mTOR Inhibitors

Temsirolimus

The pivotal trial of temsirolimus investigated its use as first-line monotherapy versus IFN-α and its use as first-line combination therapy with IFN-α versus IFN-α in patients with poor-prognosis mRCC. Key AE data related to treatment delivery indicated that 7% of temsirolimus monotherapy recipients had an AE-related treatment discontinuation, which was lower than the rate in the IFN-α

(14%) and temsirolimus plus IFN-α groups (20%) [24]. Specific attributable AEs were not reported. Dose interruption and reduction rates during temsirolimus monotherapy were 66% and 23%, respectively; those reported for IFN-α monotherapy were 68% and 39%, respectively, and those for the temsirolimus plus IFN-α combination were 82% and 30%, respectively [24]. Again, specific attributable AEs were not reported.

HRQOL was evaluated with EQ-5D scores (obtained at weeks 12 and 32, time of grade 3 or 4 AE report, relapse, progression, or study withdrawal) applied to TWiST and Q-TWiST analyses, which demonstrated that temsirolimus monotherapy conferred significantly improved quality-adjusted survival relative to IFN-α monotherapy (38% greater TWiST and 23% greater Q-TWiST with temsirolimus monotherapy versus IFN-α monotherapy). No significant differences were observed between temsirolimus plus IFN-α combination therapy and IFN-α monotherapy [32]. In a separate analysis that used last-visit EQ-5D data and a repeated-measures mixed-effect model to evaluate differences between temsirolimus monotherapy and IFN-α monotherapy, mean scores on both the EQ-5D Index and the EQ-VAS were significantly higher with temsirolimus monotherapy versus IFN-α, as was the least-square mean for on-treatment EQ-5D Index score [33].

Everolimus

The pivotal phase III trial of everolimus was a placebo-controlled trial in sorafenib- and/or sunitinib-pretreated patients; patients could also have received prior bevacizumab and cytokine therapy. Key AE data relating to treatment delivery were that 10% of everolimus recipients had an AE-related treatment discontinuation (versus 4% of placebo recipients), most commonly for pulmonary issues (pneumonitis, dyspnea, and lung disorder) and fatigue [25]. Dose interruption and reduction rates during everolimus treatment were 34% and 5%, respectively; those during placebo treatment were 15% and $<1\%$, respectively [25]. Specific AEs necessitating dose interruptions and reductions were not reported.

HRQOL was evaluated with the EORTC QLQ-C30 and the FKSI-DRS before randomization, at day 1 of each cycle, and upon study discontinuation [25, 34]. On the basis of an analysis of longitudinal mean scores on the EORTC QLQ-C30 and FKSI-DRS, HRQOL was sustained during everolimus therapy [25]. Time to definitive deterioration in HRQOL did not differ significantly between everolimus and placebo based on prespecified clinically meaningful changes in the EORTC QLQ-C30 physical functioning scale and global health status/quality-of-life score and in the FKSI-DRS [25]. At the final analysis, time to definitive deterioration in Karnofsky performance status by 10% and in FKSI-DRS by 2 units was significantly longer with everolimus (5.78 and 4.76 months, respectively) than with placebo (3.84 months for both) [34].

Table 5 provides a summary of the HRQOL data obtained with temsirolimus and everolimus in their pivotal clinical trials.

HRQOL Effects of Targeted Agents under Investigation for Treatment of RCC

Several targeted agents are currently under investigation for mRCC, including other multikinase inhibitors, dual PI3K/mTOR inhibitors, and histone deacetylase inhibitors. To date, few published reports exist on the effects of these agents on HRQOL. Trials for two such investigational agents are summarized below.

Axitinib

Axitinib is an oral inhibitor of VEGF receptors (VEGFRs) 1, 2, and 3 that achieved an overall response rate (ORR) of 44.2% (2 CR, 21 partial responses [PR]) in 52 patients with cytokine-refractory mRCC in a single-arm, open-label phase II trial [35]. HRQOL was assessed with the EORTC QLQ-C30 at baseline, day 29, day 57, and every 8 weeks thereafter to a maximum of 144 weeks of treatment, and at follow-up [36]. The rate of AE-related treatment discontinuation was 19.2% (10 patients) due to nonfatal events (specific AEs not reported). The dose reduction rate was 28.8% (15 patients) due to grade 3 AEs (diarrhea, fatigue, gastrointestinal upset, dehydration, myalgia, and gout) in 8 patients and multiple grade 2 AEs including hypertension in 7 patients [35].

HRQOL data (expressed in terms of QLQ-C30 scores to facilitate the interpretation of changes within category descriptors) revealed that over the 144-week treatment period, changes from baseline in role, cognitive, and social functioning were less than one-fourth of a category; pain and nausea and vomiting increased by less than one-fifth of a category; and diarrhea, the only symptom scale that worsened over time, increased by less than one-half of a category [36]. The magnitude of these changes suggested that most patients had limited or slight changes in functioning or symptoms with axitinib treatment. An analysis of HRQOL data of responders found that improvements in global HRQOL and social functioning and increased diarrhea were associated with tumor response [36].

In a separate phase II study of axitinib treatment of sorafenib-resistant patients, longer median PFS and OS times were associated with more favorable FKSI-15 and FKSI-DRS scores at baseline [37].

Tivozanib

Tivozanib is an oral inhibitor of VEGFRs 1, 2, and 3 that was recently reported to achieve an ORR of 25.4% in a phase II, placebo-controlled, randomized discontinuation trial of patients with locally advanced or mRCC. Median PFS was 11.8 months and was similar in treatment-naïve and refractory patients [38]. Patients naïve to VEGF-targeted therapy are currently being enrolled into a phase III trial comparing tivozanib with sorafenib, with HRQOL as a secondary endpoint [39].

Conclusions

Patient-reported outcomes are becoming increasingly important in the determination of the overall benefit of molecular targeted therapies in patients with mRCC. In phase III pivotal clinical trials, first-line therapy with sunitinib and first-line therapy with temsirolimus (in poor-prognosis patients) led to improvements in HRQOL compared with IFN-α. First-line therapy with pazopanib and second-line and subsequent therapy with sorafenib, pazopanib, and everolimus led to maintenance of HRQOL compared with placebo. Although HRQOL analyses may be potentially biased toward more efficacious therapy due to an increased frequency of complete questionnaires over a longer period of time, clinical evidence from these trials supports a strong association between tumor response and delay in tumor progression with HRQOL benefits experienced by patients with mRCC. In all cases, information gained from the patient regarding disease symptoms and treatment side effects is likely to emerge as a critical driver of treatment decision-making.

Different HRQOL tools have been used in the pivotal clinical trials of molecular targeted agents in mRCC. Some of these tools are specific to RCC, some are cancer-specific but not mRCC-specific, and still others are generic and able to assess patients with different diseases. In mRCC, disease-specific instruments are often used and may be the most focused on disease symptoms and side effects. The unique specificity of the FKSI-DRS to measure disease-related symptoms apart from treatment-related symptoms should help determine the relative effects of new treatments on HRQOL. In addition, the FKSI series of mRCC-targeted instruments contains fewer questions than generic or even cancer-specific HRQOL tools, thus requiring less time for completion.

With more second- and third-line treatment options now available for mRCC, HRQOL outcomes in earlier lines of therapy should guide treatment decisions for subsequent therapy. More research is needed to discriminate the impact of treatment-related AEs on treatment discontinuation and patient HRQOL. Because each class of agents has a unique AE profile, it is essential to determine how these AEs influence HRQOL outcomes.

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